A RESEARCH PROPOSAL

DESIGN, DEVELOPMENT AND OPTIMIZATION OF POORLY WATER SOLUBLE DRUG(S) BY USING COFORMER(S)

Submitted

For the consideration of registration for the degree of

DOCTOR OF PHILOSOPHY

In The Faculty of Pharmaceutical Sciences & Technology

By

Mr. Shivraj Sangappa Shivpuje

Under the Guidance of

Dr. Shailesh L. Patwekar
M. Pharm., Ph.D.
Assistant Professor
Department of Pharmaceutics
School of Pharmacy, SRTMU, Nanded

SWAMI RAMANAND TEERTH MARATHWADA UNIVERSITY,

NANDED-431606, (Maharashtra State), India.

(2023-2024)

DESIGN, DEVELOPMENT AND OPTIMIZATION OF POORLY WATER SOLUBLE DRUG(S) BY USING COFORMER(S)

INDEX

Sr. No.	Content	Page No.
1.	Introduction	2
2.	Literature review	6
3.	Statement of problem	9
4.	Objectives	10
5.	Methodology	10
6.	Expected research Outcomes with beneficiaries	12
7.	Time frame of dissertation	13
8.	References	14

INTRODUCTION

Solubility is the phenomenon of dissolving a solute in a solvent to form a homogeneous system. The drug's poor solubility, which leads to a high dissolution rate and low bioavailability, is a crucial consideration when developing oral dosage forms. Other dosage forms, such as parenteral dose form, are significantly impacted by the solubility of the medicines. One of the key elements in attaining the necessary medication concentration in the bloodstream to provide the intended pharmacological action is solubility [1]. When taken orally, medications with poor water solubility may require high dosages to reach the necessary therapeutic plasma concentrations. The main issue to be faced during the formulation creation of new therapeutics and generic development is low water solubility of medications. These medications have sluggish drug absorption due to their weak water solubility, which causes insufficient bioavailability and gastrointestinal toxicity. The main issue in achieving the requisite concentration of oral medications in the systemic circulation for the desired pharmacological effects is solubility. Low solubility is a problem that formulation development faces head-on [2]. The new compounds that were found in *Pinus armandii* Franch, namely 40-methoxy-2-hydroxystilbene, 7,8-dihydro-2,4 (1h,3h)-pteridinedione, and 9h-pyrido [3,4-b] indole,7-methoxy-1,9-dimethyl-, among others, have potential to be used as biological substances in the pharmaceutical industry or as drugs, owing to their antiinflammatory, anticancer, and anti-HIV activities [3].

Current research on coformers includes active substances such as glibenclamide, gliplizide, efavirenz, indomethacin glutaric acid, paliperidone, etc. have also been investigated as coformers. One strategy to alter the solubility of a drug is to modify the crystal structure by combining the active pharmaceutical ingredient with coformers to form a crystalline multicomponent system, such as cocrystals and salts [4,5].

Multicomponent crystals are solid phases that form when more than one molecule of different substances crystallize together in a crystal lattice with a certain stoichiometric ratio. In salt-form drugs, the components are arranged in a crystal lattice based on their ion pairs, whereas in cocrystals, the components are arranged through weak interactions, such as hydrogen bonds, π arrangement, or van der Waals interactions [6].

Method of Preparation of coformer cocrystal

1. Kneading method
2. Solvent evaporation method
3. Antisolvent
4. Cooling Co-Crystallization
5. Slurry Conversion
6. Neat Grinding
7. Liquid-Assisted Grinding
8. Spray-drying Method

9. Hot-melt Extrusion

Kneading method

In this procedure, a little amount of methanol or ethanol is added to the medication and coformer before being combined. The created moist mass is left to dry at ambient temperature or, if necessary, in a hot air oven [7].

Solvent evaporation method

Solvent evaporation is the most commonly used method for laboratory-scale multicomponent crystal formation, during which the drug and coformer are dissolved at a given stoichiometric ratio in a suitable solvent. Stirring is carried out under constant conditions to facilitate molecular interactions between the drug and the conformer, and then the solvent is allowed to evaporate, forming a solid, namely crystals. The main requirement of this method is that the components in forming multicomponent crystals must be completely soluble in the solvent [8].

Antisolvent

This method represents an alternative to solvent evaporation and cooling techniques for the formation of cocrystals with lower solubility. In addition, the process can be performed at ambient temperature and consumes less energy than cooling and solvent evaporation methods. Several studies have investigated techniques involving antisolvents to make it easier to control the properties of crystals and increase their purity and yield [9].

Cooling Co-Crystallization

Cooling co-crystallization is based on temperature variations and generally uses a reactor to mix components and solvents. The system is then heated to achieve dissolution of the two components. Saturation is achieved by reducing the temperature. This approach can be used with a complementary phase diagram to identify thermodynamically stable regions and predict potential cocrystal formation. In addition, by analyzing the kinetic pathways of the compounds and the degree of saturation, it is possible to determine the optimal conditions [10].

Slurry Conversion

This method involves the formation of cocrystals by adding excess cocrystal components to the solvent. In this method, each component dissolves slowly to form a complex, which may result in the formation of cocrystals. Slurry conversion is an alternative method of producing cocrystals, the coformers of which are insufficiently soluble. The slurry conversion method is simple and includes the crystallization of pure cocrystals with a small quantity of solvent. This approach can be used to produce cocrystals only if the cocrystal is the most thermodynamically stable form relative to other crystalline forms. As a result, this approach can also be used to screen for the most stable crystal formations [11].

Neat Grinding

Neat grinding, also called dry grinding or solid grinding, consists of mixing the stoichiometric cocrystal components together in a solid state and grinding them either manually using a mortar and pestle or mechanically using a ball mill or vibratory mill. Mefenamic acid cocrystals with nicotinamide coformers, itraconazole

co-crystals with succinic acid coformers, aspartic acid, serine, proline, and glycine were obtained by this technique [12].

Liquid-Assisted Grinding

Liquid-assisted grinding involves the addition of a small amount of solvent to a dry solid prior to the start of the grinding process. The solvent acts as a catalyst, assisting in the formation of multicomponent crystals and must persist throughout the milling process. Liquid-assisted grinding results in more efficient multicomponent crystal formation and an increase in cocrystal formation kinetics compared to neat grinding [10].

Spray-drying Method

Spray drying is a rapid method used to engineer a solid state, producing a dry powder from a solution or suspension using a stream of hot air. For coformer-pharmaceutically active substance solubility systems, in pure crystalline multicomponents cannot be formed acid, and caffeine–glutamic acid cocrystals are examples of incongruent systems that cannot produce pure cocrystals by the solvent evaporation method but manage to form pure crystals when the spray drying-method is used [13].

Hot-melt Extrusion

Hot melt extrusion can be employed for the preparation of co-crystals as a continuous manufacturing process in a single step. In this method, the co-crystals are prepared by providing heat energy with high intense mixing to the drug and coformer to become miscible in the molten stage. The criteria for this method are the drug and coformer, which should be miscible at the molten stage [14-16].

Selection of Coformer

The selection of coformers is a major challenge the development of pharmaceutical multicomponent crystals that are compatible with pharmaceutically active substances. The general strategy used in selecting coformers is tactless experimental approaches whereby a predetermined number of candidates from compounds listed in the generally regarded as safe (GRAS) list are used to form multicomponent crystals [26]. The requirements for a substance to be used as a coformer are that it must be safe and non-toxic and have no side effects. Coformers must be on the FDA's "Everything added to food in the United States" (EAFUS) list or on the generally regarded as safe (GRAS) list. [27].

Several approaches can be adopted to select coformers, including the molecular synthon approach using the Cambridge Structural Database (CSD). CSD is a computer-based approach used to find pairs of coformers and active pharmaceutical ingredients to form multicomponent crystals, as well as reduce costs and experimental time to increase research efficiency [17,18].

pKa is a simple approximation used to predict the formation of multicomponent crystals. In general, salt formation occurs when there is a difference between the pKa of a base and the pKa of an acid (ΔpKa) > 3, whereas pKa < 0 results in the formation of cocrystals [19].

The Hansen solubility parameter is another important approach used to measure drug and coformer miscibility for crystallization under a multicomponent approach. According to the Hansen solubility parameter, the total cohesive energy of the liquid is divided into contributions from atomic dispersion (δd), dipole–dipole/polar interactions (δp), and hydrogen bonding (δh). Cohesive energy is the sum of van der Waals bonding forces, covalent bonds, hydrogen bonds, and ionic bonds. [20].

In the selection of coformers, functional groups are needed to form molecular synthon bonds to predict the formation of cocrystals. A molecular synthon is a structural unit within a supermolecule that can be formed through known or imagined intermolecular interactions. Supramolecular synthons are divided into two classes, namely supramolecular heterosynthones and supramolecular homosynthones. Supramolecular heterosynthone is formed by covalent binding of different molecular fungtional groups but complements, for example, carboxylic acid–pyridine and carboxylic–amide. Homosynthone is produced by the formation of the same dimer formation C=O..H-N hydrogen binding [28].

For example, the interaction between the carboxylic acid group and the amide is occurs in two or more compounds with different but complementary functions. Meanwhile, supramolecular homosynthone is a formed between two similar compounds with the same functional group as the interaction between an amide group and an amide or a carboxylic acid group with a carboxylic acid [18].

In a study conducted by Prasad et al., cocrystal formation in an ornidazole system with para-amino acid and para-hydroxybenzoic acid coformers was analyzed as follows. For a binary system with strong hydrogen-bonding groups, the primary supramolecular growth unit must be at least three molecules long to form a cocrystal. [21].

Advantages of coformer

- The physical and chemical properties of an API like solubility, melting point, bioavailability, stability, dissolution rate can be enhanced by cocrystals without breaking or making the covalent bonds.
- One of the techniques to improve solubility is salt formation which requires acidic, basic and ionisable site, whereas, cocrystals can be prepared even in the absence of acidic, basic or ionisable group in an API [22].

Disadvantages of coformer

- Suitable solvent selection is a tedious process.
- Lower melting points cocrystal is obtained by weak carboxylic acids, which can result in higher levels of amorphous API.
- It is difficult to maintain processing parameters like temperature and agitation [22].

LITERATURE REVIEW

Iyan Sopyan et. al. (2023), Multicomponent crystallization is a method that can modify the physicochemical properties of Carvedilol (CVD), thereby increasing its solubility. Based on in silico screening the coformers (Benzoic Acid, Isonicotinamide, and Saccharin) showed non-covalent interactions with CVD, so the multicomponent crystal preparation of CVD by solvent evaporation method used these coformers with mole ratios of 1:1, 1:2, and 2:1. Multicomponent CVD:Isonicotinamide (1:2) exhibits increased saturation solubility of up to 140 mg/L and increased dissolution of up to 99.48%. The infra-red (IR) spectrum showed a peak shift, a thermogram pattern that was different from the DSC results, and a new peak on the XRD multicomponent crystal diffractogram indicating the formation of a new solid phase compared to pure Carvedilol. Therefore, the formation of multicomponent crystals can increase the solubility and dissolution rate of CVD, and all characteristics indicate the presence of interaction between CVD and Isonicotinamide, and the formation of a new solid phase [23].

Aghara M. et. al. (2023), In this article, we demonstrate the application of cooling crystallization to generate novel solid forms of drug-coformer cocrystal complexes. This approach enabled us to replicate several cocrystal phases previously reported for pharmaceutical drugs. Additionally, we successfully produced a new solid mixture comprising the drug luliconazole and coformers such as mannitol and menthol, as well as a potential new crystal form of the cocrystal luliconazole:menthol and luliconazole:mannitol. By utilizing cooling crystallization, we were able to prepare phase-pure LCZ-MNT and LCZ-MNL cocrystals [24].

Mehta J. et. al. (2023), The present investigation was aimed at preparing ketoconazole cocrystals using phenolic acid coformers. The slow solvent evaporation method was used to prepare ketoconazole cocrystal. The results of the DSC study, SEM study, and PXRD study confirmed the formation of a new crystalline phase. Molecular docking results show cocrystal requires less binding energy and more binding affinity with sterol 14α-demethylase compared to pure ketoconazole and PHBA and has improved solubility and dissolution [25].

Sapana P. Ahirrao et. al. (2022), Etodolac (ETD) is a non-steroidal anti-inflammatory drug (NSAID) given in rheumatoid arthritis treatment. As it comes under BCS class II drug hence it exhibits low water solubility. Also, its dissolution rate-limited oral absorption results in delayed onset of action. The Novel approach in the solubility enhancement field; crystal engineering was preferred to prepare pharmaceutical cocrystals of etodolac with GRAS (generally recognized as safe) molecules. Pharmaceutical cocrystals of etodolac were prepared with p-hydroxybenzoic acid and glutaric acid with the drug: coformer ratio 1:1 and 1:2. Cooling cocrystallization was used to prepare etodolac cocrystals. Cocrystal formulations were characterized by saturation solubility study, in-vitro dissolution studies, and stability study. Cocrystal was also characterized by analytical parameters like Fourier transform infrared spectroscopy (FTIR), powder X-ray diffraction (PXRD), and differential scanning calorimetry (DSC). Optimized Cocrystal formulation dissolved more rapidly and their equilibrium solubility is greater than the plain drug [26].

Marika Turek et. al. (2021), Physicochemical properties, in particular solubility and the associated bioavailability, are key factors in determining efficacy of poorly water-soluble drugs, which constitute 40% of new drugs in the market, and improving them is an important challenge for modern pharmacy. A recent strategy to achieve this goal is formation of stable co-amorphous solid dispersions with co-formers of low molecular weight. Here, the amorphization strategy was applied for low-soluble anti-hypertensive valsartan (VAL), an angiotensin II receptor blocker, and nicotinamide, which exhibits lung- and cardio-protective effects. Through interactions with the renin−angiotensin−aldosteron system, VAL may be used to treat both hypertension and the current pandemic coronavirus SARSCoV-2 infection. Using mechanochemical and liquid- and solidstate approaches, solvated co-amorphous solid dispersions of VAL with nicotinamide were obtained. They were characterized by spectroscopic, thermal, and X-ray analyses. The density functional theory, quantum theory of atoms in molecules, and non-covalent interaction index calculations revealed the presence of two types of hydrogen bonds between VAL and NIC (i.e., N−H···O and O− H···O). One of them had a partially covalent character, which caused conformational changes in the flexible VAL molecule, restricting contribution of the tetrazolyl N−H donor and thus limiting the possibility of co-crystal formation. The recognized VAL/ NIC1- and VAL/NIC2-type heterodimeric interactions were responsible for the excellent durability of the solid compositions and up to 24-fold better solubility than VAL alone. The synthesized dispersions constitute a new class of dually acting drugs, containing an active pharmaceutical ingredient (VAL) and supporting nutraceutical (nicotinamide) [27].

Sunil Kumar Gohel et. al. (2021), Muscle relaxant and pain reliever metaxalone (MET) is a biopharmaceutical classification systems (BCS) class II drug with poor aqueous solubility and high permeability. The presence of an aromatic skeleton and cyclic carboxamate moiety are the probable reasons for the decreased aqueous solubility, which impacts on its low bioavailability. A high dose (800 mg) of the drug often creates adverse side effects on the central nervous system that needs urgent remedy. Cocrystallization of MET with nicotinamide (NAM), salicylamide (SAM), and 4-hydroxybenzoic acid (HBA) resulted in multicomponent solids that were characterized by PXRD, DSC and single crystal X-ray diffraction. Cocrystals with SAM and NAM form 2D isostructural cocrystals, whereas with HBA the result is a differently packed cocrystal hydrate (or anisole hemisolvate) depending upon the crystallization medium. Similar to the reported MET cocrystals, these cocrystals also confirm the preference for an imide/imide homosynthon in the drug. The dominance of the drug–drug homodimer over drug-coformer heterodimers was demonstrated based on binding energy calculations. Further, powder dissolution experiments in pH 6.8 phosphate buffer indicate that the cocrystals improved the apparent solubility compared to the native drug by 3–9 fold. The absence of stronger heterosynthons between MET and the coformers, their lower melting points and the high solubility of the coformers are the probable reasons for the enhanced solubility of the bioactive component. The MET–NAM cocrystal exhibited the highest solubility/dissolution rate among the three binary solid forms, which may offer improved bioavailability and a lower dose with minimal side effects [28].

J. Thimmasetty et. al. (2020), The aim of the study was to improve bioavailability of paliperidone, a class II drug, via cocrystallization with a peep to the effect of HPMC as a precipitation inhibitor (PPI). An attempt was made to prepare paliperidone cocrystals with benzamide, boric acid, nicotinamide, and PHBA as coformers after the prediction of cocrystal formation using Hansen solubility parameter (HSP) as a prediction tool. The cocrystals were prepared, with a 1:1Mratio of drug and coformer, by the solvent evaporation method. The prepared cocrystals were characterized by melting point, saturation solubility and in vitro drug release along with instrumental analytical techniques such as FTIR, DSC, PXRD, and SEM. The formation of paliperidone cocrystals using benzamide, nicotinamide, and PHBA was confirmed, as predicted by HSP, by collective assessment of the results. On the other hand, the formation of paliperidone cocrystals by boric acid could not be proved. These findings revealed the suitability of HSP as a cocrystal formation prediction tool. In spite of this, the successfully prepared paliperidone-PHBA (PAL-PHBA) cocrystals had shown a tremendous increase in their solubility (0.115 mg/ml to 16.29 mg/ml, 141.6 fold) and dissolution (49%in 60min to100%release in 30min) when compared to the pure drug. Therefore, these cocrystals further studied for paliperidone bioavailability in albino rabbits, in the presence and absence of HPMC as a PPI. The results showed an improvement in the bioavailability of paliperidone in the presence of precipitation inhibitor. Conclusion Thus cocrystallization and precipitation inhibition technique increases the bioavailability of the drug [29].

Ari Wahyudi et. al. (2020), Mefenamic acid is an analgesic non-steroidal anti-inflammatory drug (NSAID) that is categorized as Biopharmaceutical Classification System (BCS) class II drug. Cocrystallization of mefenamic acid (MFA) with nicotinamide (NIC) has been reported to enhance the solubility of MFA for about 2.56 times higher than pure MFA. As a part of MFA-NIC development in pharmaceutical dosage form, we reported the improvement of mechanical properties of MFA-NIC cocrystal based on the presence of slip planes in crystal structure. The research was initially by synthesizing and characterizing the cocrystal by using X-ray diffraction analysis, and was followed by the investigation of the mechanical properties of MFA and its cocrystal, i.e. tensile strength and deformation parameter. The correlation of crystal structure with mechanical properties was determined by crystal packing motif and slip plane analysis from single crystal data by using Mercury 3.6. The tensile strength of MFA was acceptance at 20.0 MPa, and dropped at more than 25.0 MPa. A better tableting performance was observed in MFA-NIC cocrystal which had the tensile strength 1.5 times higher than MFA at 12.5 MPa and gradually increased with an increasing pressure up to 2.5 times at 22.5 MPa. The flat slip plane of MFA-NIC cocrystal was predicted as the key factor in the improvement of its mechanical properties, compared to zigzag slip plane of MFA. In conclusion, MFA-NIC cocrystal had the better mechanical properties than pure MFA due to its flat slip plane and it becomes potential to be explored in further development of solid dosage form [30].

Luan F. Diniz et. al. (2020), Furosemide (FSM) is a biopharmaceutical classification system (BCS) class IV drug, being a potent loop diuretic used in the treatment of congestive heart failure and edema. Due to its low solubility

and permeability, FSM is known for exhibiting poor oral bioavailability. In order to overcome or even minimize these undesirable biopharmaceutical attributes, in this work we have focused on the development of more soluble and permeable multicomponent solid forms of FSM. Using solvent evaporation as crystallization method, a salt and a cocrystal of FSM with imidazole (IMI) and 5-fluorocytosine (5FC) coformers, named FSM-IMI and FSM-5FC, respectively, were successfully prepared. A detailed structural study of these new solid forms was conducted using single and powder X-ray diffraction (SCXRD, PXRD), Fourier Transform Infrared (FT-IR) and proton Nuclear Magnetic Resonance (1H NMR) spectroscopy and thermal analysis (thermogravimetry, differential scanning calorimetry and hot-stage microscopy). Both FSM-IMI and FSM-5FC showed substantial enhancements in the solubility (up 118-fold), intrinsic dissolution (from 1.3 to 2.6-fold) and permeability (from 2.1 to 2.8-fold), when compared to the pure FSM. These results demonstrate the potential of these new solid forms to increase the limited bioavailability of FSM [31].

Ilma Nugrahani et. al. (2020), This research dealt with the multicomponent crystal developed from diclofenac potassium and L-proline to improve the pharmaceutical performance of this anti-inflammatory drug. Slow evaporation of the component mixture at a 1:1 M ratio, supported by ultrasonication, yielded a new salt cocrystal, which was characterized using thermal analysis, Karl Fischer titration, infrared spectrophotometry, powder diffractometry, and single crystal diffractometry. This salt cocrystal was confirmed as a tetrahydrate that comprised diclofenac potassium, L-proline, and water (1:1:4), named DKPH. The new salt cocrystal enhanced the solubility of diclofenac potassium by up to 3.56 folds and accelerated the intrinsic dissolution rate of 3.36 folds. It was supported by the solid and solution phase intermolecular interaction study. A different phase, which indicated a monohydrate form of the salt cocrystal, was found from the low humidity chamber during the isotherm sorption study. However, the tetrahydrate, DKPH, was proven as a stable form under ambient conditions [32].

STATEMENT OF PROBLEM

Even though a lot of research has been done on this subject, medication solubility and bioavailability remain key issues in modern medicine. Our goal is to select a system that improves the solubility and bioavailability of BCS class II and IV drugs by using coformer.

SIGNIFICANCE

As a result of the drawbacks of this system, such as its low solubility, dissolution, and need for frequent drug administration, coformer was chosen as the answer. The solubility problem prevents standard therapy from being a site-targeting therapy. Making cocrystal by using coformer is one of the most advanced techniques for making medications that aren't very soluble in water more soluble.

OBJECTIVES

This research will be conducted to achieve following objectives:

- For the improvement of solubility and bioavailability of poorly water-soluble drug.

- To prepare complex of poorly water-soluble drug and coformer by suitable methods.
- Formulation development of poorly water-soluble drug cocrystal.
- To improve the in-vitro dissolution rate of the poorly water-soluble drug.
- To evaluate the in-vivo of developed drug cocrystal formulation.

HYPOTHESIS

BCS class-II and class-IV drugs that are poorly water soluble have high permeability and low water solubility, and low permeability and low water solubility, respectively. These characteristics are the cause of the drugs slow dissolving rate and, ultimately, variable absorption. The formulation of poorly water-soluble medication and conformer cocrystal using a variety of techniques, including physical mixing, melting, and kneading, to increase the rate of dissolution in order to obtain a faster rate of dissolution, a better absorption profile, and the desired pharmacological outcome.

METHODOLOGY

Phase I: Preformulation studies

1) *Selection of drug:* In present research work BCS class II & IV such as poorly water soluble have high permeability and low water solubility, and low permeability and low water solubility, respectively. will be selected & it suitability for coformer cocrystal will be assessed.

2) *Preformulation studies:* The physicochemical properties of the actives and other excipients will be confirmed.

    a. *Analytical Method Development*: A suitable UV method and HPLC method will be developed and validated as per ICH guidelines.

    b. *Drug – Excipient Compatibility Studies:* Selected drug candidate and excipients compatibility shall be investigated using Differential Scanning Calorimetry (DSC) and Infrared (IR) spectroscopy. Pure drug, excipients and Physical mixture of the drug and excipients shall be subjected to such study to determine the compatibility between the drug and selected excipients.

3) *Experimental design*:

    a. *Selection of coformer and excipients for various formulation functions:* various excipients will be screened and selected to meet desired formulation requirements to obtain the enhance drug solubility, to ensure the dosage form is stable and suitable for application.

Preparation of coformer cocrystal of poorly water-soluble drug

As per the suitability of drug and selected coformer, the drug shall be complex with coformer in the form of various drug release systems like granules or microspheres or cocrystal etc. shall be fabricated. Choice of the

excipient shall be dependent on the nature of the drug and type of formulation. Side specific formulation will be developing with different ratio with drug.

The drug and coformer cocrystal formulations will be develop by using techniques like hot melt extrusion, kneading, spray drying, spray congealing, emulsification solvent evaporation etc. and combination of these techniques with other manufacturing processes known in the field of formulation development.

A. Optimization of formulation:

The developed formulations shall be optimized for the process parameters like mixing time, temperature, overall process parameters like rate of addition, speed of stirrer etc. or other relevant parameters as applicable in the selected formulation method. The critical process parameters shall be selected and their impact on the critical material attributes of the drug substance and formulation components shall be studied and reported.

The critical formulation attributes like bulk density, particle size distribution, morphology of the particles shall be optimized to fit the ideal requirements of the coformer cocrystal. Formulation parameters like drug content, content uniformity, and drug release will be determined.

Suitable statistical approaches shall be applied to optimize the formulation process and formulation critical material attributes. The use of software's like Minitab and Design experts shall be utilized for the same.

The selection of delivery vehicle like gel, tablet, capsule with coformer shall be optimized keeping in mind the intended application in the site of action.

Phase II: Characterization

A. *Characterization of optimized formulation:* Optimized formulation shall be characterized for the parameters like drug content, solubility using validated UV or HPLC methods, physical properties like bulk density, tapped density will be determined using USP listed methods. Drug loaded particles will also be characterized by Fourier transform infrared (FTIR), differential scanning calorimetry (DSC) and X-ray diffraction analysis (XRD).

B. *Drug content:* The test solution was made by dissolving 10 mg of solid dispersions in 10 ml of volumetric flask using methanol. A volume of 10 ml was created by pipetting out 0.1 ml of this solution. Similar to this, a standard solution was also made, and the finished product was scanned using methanol as a blank at a particular wavelength.

C. *Solubility study:* The drug's solubility was tested in distilled water and other physiological pH solution [40]. To create the saturated solution, more medication was added to distilled water and other physiological pH solution. Then, using distilled water and other physiological pH solution as a blank, solutions were filtered and scanned at a specified wavelength [41].

D. Phase solubility study: Phase solubility testing involved combining medication with aqueous solutions containing various coformer concentrations at 5%, 10%, 15%, 20%, and 25% w/v. Using an orbital shaker, the

sealed flasks were shaken for 48 hours at room temperature. The resulting solutions were then filtered using filter paper with 0.45 m pore size. The final filtrate was then examined using a UV photo spectrometer at a specific wavelength with pure water used as a control. Using equation [41], one can calculate the apparent stability constant.

$$Ks = \frac{\text{slope}}{(1- \text{slope})\ \text{intercept}}$$

Where,

Ks = Apparent stability constant of each drug-carrier combination.

Intercept = Solubility of drug at 0% carrier.

E. *In-vitro diffusion studies of drug from the developed formulations*: These shall be carried out using suitable dissolution apparatus in suitable dissolution media and statistical analysis will be applied.

F. *Percentage yield:* Percentage yield of solid dispersion by using various ratio of drug and carrier was determined by using formula.

$$\% \text{ yield} = \frac{\text{Practical yield}}{\text{Theoretical yield}} X100$$

Phase III: In-vivo Characterization of Formulation

Expected research Outcomes with beneficiaries:

- The cocrystal-based approach for solubility enhancement of low soluble drug using suitable coformer and method will improve solubility with the use of low-cost techniques compared to novel non-economical techniques.
- Solubility enhancement will be beneficial for the reduction of dose or beneficial for absorption and good patient compliance.
- Research outcome will help pharma industry in terms of collaboration or funding or patents.
- High-quality Publications in Journals listed in globally recognized databases.

Originality:

In the current literature the researchers had developed the platform for solubility enhancement with various techniques and excipients.

- The proposal aims to develop simple Formulation by using suitable new technology to reduce the cost.

TIME FRAME OF DISSERTATION

Activity/Work elements	Time schedule (months)					
	0-6	7-12	13-18	19-24	25-30	31-36
Literature Survey						
Purchase of chemicals, and raw materials. Preformulation Study of drug, and characterization of raw materials.						
Solubility enhancement by best suitable technologies. optimization of the drug-coformer ratio using design expert software.						
Characterization of drug-coformer cocrystal.						
Development and optimization of formulation.						
In-vivo Characterization of Formulation.						
Compilation of Work & Thesis Writing.						

REFERENCES:

1. V. R. Vemula, V. Lagishetty, and S. Lingala. Solubility enhancement techniques. Int. J. Pharm. Sci. Rev. 2010; 5:678.
2. D. Sharma, M. Soni, S. Kumar, and G. D. Gupta. Solubility enhancement—eminent role in poorly soluble drugs. Res. J. Pharm. Technol. 2009; 2(2): 220–224.
3. Ge S., Liang Y., Zhou C., Sheng Y., Zhang M., Cai L., Zhou Y., Huang Z., Manzo M. and Wu C. The potential of Pinus armandii Franch for high-grade resource utilization. Biomass-Bioenergy. 2022; 158: 106345.
4. Kumar S. and Nanda A. Approaches to Design of Pharmaceutical Cocrystals: A Review. Mol. Cryst. Liq. Cryst. 2018; 667: 54–77.
5. Elkholy N.E., Sultan A.A., Elosaily G.H. and El Maghraby G.M. Acetone-assisted co-processing of meloxicam with amino acids for enhanced dissolution rate. Pharm. Dev. Technol. 2020; 25: 882–891.
6. Kiguchiya A., Teraoka R., Sakane T. and Yonemochi E. A New Method for Classification of Salts and Cocrystals Using Solid-State UV Spectrophotometry. Chem. Pharm. Bull. 2019; 67: 945–952.
7. Sheetal Shewale, A. S. Shete, R. C. Doijad, S. S. Kadam, V. A. Patil And A. V. Yadav. Formulation and Solid State Characterization of Nicotinamide-based Co-crystals of Fenofibrate: Indian J Pharm Sci 2015; 77(3): 328-334.
8. Barikah K. Traditional and Novel Methods for Cocrystal Formation: A Mini Review. Syst. Rev. Pharm. 2018; 9: 79–82.
9. Kudo S. and Takiyama, H. Solubility Determination for Carbamazepine and Saccharin in Methanol/Water Mixed Solvent: Basic Data for Design of Cocrystal Production by Antisolvent Crystallization. J. Chem. Eng. Data 2018; 63: 451–458.
10. Rodrigues M., Baptista B., Lopes J.A. and Sarraguça M.C. Pharmaceutical cocrystallization techniques. Advances and challenges. Int. J. Pharm. 2018; 547: 404–420.
11. Aitipamula S., Banerjee R., Bansal A.K., Biradha K., Cheney M.L., Choudhury A.R., Desiraju G.R., Dikundwar A.G., Dubey R. and Duggirala N. Polymorphs, Salts, and Cocrystals: What’s in a Name? Cryst. Growth Des. 2012; 12: 2147–2152.
12. Kozak A., Marek P.H. and Pindelska E. Structural Characterization and Pharmaceutical Properties of Three Novel Cocrystals of Ethenzamide with Aliphatic Dicarboxylic Acids. J. Pharm. Sci. 2018; 108: 1476–1485.
13. Alhalaweh A. and Velaga S.P. Formation of Cocrystals from Stoichiometric Solutions of Incongruently Saturating Systems by Spray Drying. Cryst. Growth Des. 2010; 10: 3302–3305.

14. Gajda M, Nartowski KP, Pluta J and Karolewicz B. Continuous, one-step synthesis of pharmaceutical cocrystals via hot melt extrusion from neat to matrix-assisted processing - State of the art. Int J Pharm. 2019; 558: 426–40.
15. Kumar S. and Nanda A. Pharmaceutical cocrystals: an overview. Indian J Pharm Sci. 2017; 79(6): 858–71.
16. Savjani JK. Co-crystallization: an approach to improve the performance characteristics of active pharmaceutical ingredients. Asian J Pharm. 2015; 9(3): 147–51.
17. Qiao N., Li M., Schlindwein W., Malek N., Davies A. and Trappitt G. Pharmaceutical cocrystals: An overview. Int. J. Pharm. 2011; 419: 1–11.
18. Ross S.A., Lamprou D.A. and Douroumis D. Engineering and manufacturing of pharmaceutical co-crystals: A review of solvent-free manufacturing technologies. Chem. Commun. 2016; 52: 8772–8786.
19. Cruz-Cabeza A.J. Acid–base crystalline complexes and the pKa rule. Cryst Eng Comm 2012; 14: 6362–6365.
20. Salem A., Nagy S., Pál S. and Széchenyi A. Reliability of the Hansen solubility parameters as co-crystal formation prediction tool. Int. J. Pharm. 2019; 558: 319–327.
21. Prasad K.D., Cherukuvada S., Stephen L.D. and Row T.N.G. Effect of inductive effect on the formation of cocrystals and eutectics. Cryst Eng Comm 2014; 16: 9930–9938.
22. Tomislav Friščić, William Jones, Benefits of cocrystallisation in pharmaceutical materials science: an update, Journal of Pharmacy and Pharmacology, 2010; 62(11): 1547–1559.
23. Sopyan I., Layyareza R.T., Megantara S. and Marvita S.S. Carvedilol solubility enhancement by multicomponent crystallization with coformers of benzoic acid, isonicotinamide, and saccharin. Pharmacia. 2023; 70(2): 283–290.
24. Aghara M. and Dudhat K. Solubility and Dissolution Enhancement of Luliconazole by a Cocrystal Engineering Technique with Different Coformers. J Pharm Innov. 2023; 18: 1701–1712.
25. Mehta J., Borkhataria C. and Patel A. Para-Hydroxy Benzoic Acid Coformer Enable Enhanced Solubility, Dissolution, and Antifungal Activity of Ketoconazole Cocrystals. J Pharm Innov. 2023; 18: 1602–1615.
26. Ahirrao S.P., Sonawane, M.P., Bhambere D.S., Udavant P.B., Ahire E.D., Kanade R. and Kuber D. Cocrystal Formulation: A Novel Approach to Enhance Solubility and Dissolution of Etodolac. Biosci. Biotechnol. Res. Asia 2022; 19: 111–119.
27. Turek M., Ró˙zycka-Sokołowska E., Koprowski M., Marciniak B. and Bałczewski P. Role of Hydrogen Bonds in Formation of Coamorphous Valsartan/Nicotinamide Compositions of High Solubility and Durability with Anti-hypertension and Anti-COVID-19 Potential. Mol. Pharm. 2021; 18: 1970–1984.
28. Gohel S.K., Palanisamy V., Sanphui P., Prakash M., Singh G.P. and Chernyshev V. Isostructural cocrystals of metaxalone with improved dissolution characteristics. RSC Adv. 2021; 11: 30689–30700.

29. Thimmasetty J., Ghosh T., Nayak N.S. and Raheem A. Oral Bioavailability Enhancement of Paliperidone by the use of Cocrystalization and Precipitation Inhibition. J. Pharm. Innov. 2020; 16: 160–169.
30. Wahyudi A., Utami D. and Setianto A.B. The crystal packing and slip plane analysis in mechanical properties improvement of mefenamic acid by cocrystallization with nicotinamide coformer. Commun. Sci. Technol. 2020; 5: 93–97.
31. Diniz L.F., Carvalho P.S., Pena S.A.C., Gonçalves J.E., Souza M.A.C., de Souza Filho J.D., Bomfim Filho L.F.O., Franco C.H.J., Diniz R. and Fernandes C. Enhancing the solubility and permeability of the diuretic drug furosemide via multicomponent crystal forms. Int. J. Pharm. 2020; 587: 119694.
32. Nugrahani I., Komara S.W., Horikawa A. and Uekusa H. Composing Novel Diclofenac Potassium and l-Proline Salt Cocrystal as a Strategy to Increase Solubility and Dissolution. J. Pharm. Sci. 2020; 109: 3423–3438.

Date:

Place:

Mr. Shivraj S. Shivpuje — **Research Scholar**

Dr. Shailesh L. Patwekar — **Research Supervisor**